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(54) Title: GYNECOLOGIC ENDOVASCULAR EMBOLOTHERAPY METHODS

(57) Abstract

This invention is directed to novel methods for gynecologic embolotherapy by endovascular embolization with a fluid embolic composition which *in situ* in the blood vessel forms a coherent solid mass.

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GYNECOLOGIC ENDOVASCULAR EMBOLOTHERAPY METHODS

BACKGROUND OF THE INVENTION

Field of the Invention

This invention is directed to novel methods for gynecologic embolotherapy by endovascular embolization with a fluid embolic composition which *in situ* in the blood vessel forms a coherent solid mass. The methods provide precise directed delivery of embolic fluid compositions and are particularly suited for treating uterine fibroids.

In a preferred embodiment, the fluid embolic compositions comprise a biocompatible polymer, a biocompatible solvent and a biocompatible water insoluble contrast agent. In a most preferred embodiment, the contrast agent is characterized by having an average particle size of about 10 μm or less.

References

The following publications are cited in this application as superscript numbers:

[1] Mandai, et al., "Direct Thrombosis of Aneurysms with Cellulose Acetate Polymer", *J. Neurosurg.*, 77:497-500 (1992)

[2] Kinugasa, et al., "Direct Thrombosis of Aneurysms with Cellulose Acetate Polymer", *J. Neurosurg.*, 77:501-507 (1992)

[3] Casarett and Doull's *Toxicology*, Amdur et al., Editors, Pergamon Press, New York, pp. 661-664 (1975)

[4] Greff, et al., *U.S. Patent No. 5,667,767* for "Novel Compositions for Use in Embolizing Blood Vessels", issued September 16, 1997

[5] Greff, et al., *U.S. Patent No. 5,580,568* for "Cellulose Diacetate Compositions for Use in Embolizing Blood Vessels", issued December 3, 1996

[6] Kinugasa, et al., "Early Treatment of Subarachnoid Hemorrhage After Preventing Rerupture of an Aneurysm", *J. Neurosurg.*, 83:34-41 (1995)

[7] Kinugasa, et al., "Prophylactic Thrombosis to Prevent New Bleeding and to Delay Aneurysm Surgery", *Neurosurg.*, 36:661 (1995)

[8] Taki, et al., "Selection and Combination of Various Endovascular Techniques in the Treatment of Ciant Aneurysms", *J. Neurosurg.*, 77:37-42 (1992)

[9] Evans, et al., *U.S. Patent Application Serial No. 08/802,252* for "Novel Compositions for Use in Embolizing Blood Vessels", filed February 19, 1997.

[10] Castaneda-Zuniga, et al., *Interventional Radiology*, in Vascular Embolotherapy, Part 1, 1:9-32, Williams & Wilkins, Publishers (1992)

[11] Rabinowitz, et al., *U.S. Patent No. 3,527,224*, for "Method of Surgically Bonding Tissue Together", issued September 8, 1970

[12] Hawkins, et al., *U.S. Patent No. 3,591,676*, for "Surgical Adhesive Compositions", issued July 6, 1971

[13] Evans, et al., *U.S. Patent Application Serial No. 08/655,987*, for "Methods for the Reversible Sterilization of Male Mammals, filed May 31, 1996

[14] Evans, et al., *U.S. Patent Application Serial No. 08/656,394*, for "Methods for the Reversible Sterilization of Female Mammals, filed May 31, 1996

[15] Evans, et al., *U.S. Patent No. 5,695,480*, for "Novel Embolizing Compositions, issued December 9, 1997

[16] Goodwin, et al., "Preliminary Experience with Uterine Artery Embolization for Uterine Fibroids," *J. Vasc. Interven. Radiol.* 8:517-526 (1997)

[17] Vedantham, et al., "Uterine artery embolization: An underused method of controlling pelvic hemorrhage," *Am. J. Obstet. Gynecol.* 176(4):938-948 (1997)

The disclosures of each of the above publications, patents and patent application are herein incorporated by reference in their entirety to the same extent as if the language of each individual publication, patent and patent application were specifically and individually included herein.

Background of the Invention

Gynecologic embolotherapy may be conducted for a variety of purposes including the treatment of postpartum and postcaesarean bleeding, the treatment of postsurgical vaginal bleeding, the prevention and/or treatment of hemorrhage from ectopic pregnancy, prophylactically prior to myomectomy and in obstetrical patients at high risk for bleeding, such as those patients with placenta previa, placenta accreta, uterine fibroids and twin fetal death. Gynecological embolotherapy, however, has only been used for non-malignant conditions and the literature reports the use of polyvinyl alcohol (PVA) particles of sizes varying from 150 to 700 μm as the embolizing agents.[16]

Complications arising from endovascular embolization using PVA particles include complications of angiography, pelvic infection, pelvic pain and ischemia. The incidence of postembolization pelvic pain has been attributed to the size of the PVA particles employed with smaller particles associated with higher incidences of pelvic pain. In addition, such small particles are not visualible under fluoroscopy and, accoridngly, can migrate during injection causing unwanted ischemia and necrosis.[17] Small particles

such as PVA can also compact and migrate resulting in incomplete embolization and recanalization. [16]

Notwithstanding the use of PVA particles as the embolizing agent, uterine fibroid shrinkage was noted in patients with fibroids following gynecological embolization of these patients for acute bleeding, leading to the establishment of several clinical programs which use uterine artery embolization for the treatment of uterine fibroids. Clinical success of uterine artery embolization (defined as improvement in bleeding, pain and mass effect such that no further operative therapy is required) is good. Fibroid size is reduced, on average, by about 50% in patients undergoing uterine artery embolization.[16,17]

In view of the above, gynecological embolization methods for treatment and/or prevention of gynecological and/or obstetrical bleeding disorders which provide for delivery of substantially fluid compositions (e.g., compositions comprising particles having maximum average particle size of less than 100 μm) to be delivered to the uterine artery would be beneficial as these compositions. Moreover, the formation *in situ* of a solid coherent mass in the artery would mitigate against the adverse effects reported in the literature with current uterine embolic procedures.

This invention is directed to endovascular uterine embolization methods which employ fluid embolization compositions. Such compositions preferably comprise a biocompatible solvent, a biocompatible polymer and a contrast agent which is preferably a water insoluble contrast agent of less than 100 μm in average particle size and more preferably less than 10 μm in average particle size.

Heretofore, such embolization compositions have been employed in vascular embolization for treating aneurysms, tumors, arteriovenous

malformations (AVM), arteriovenous fistula (AVF) and uncontrolled bleeding and the use of water insoluble, radiopaque contrast agent in these compositions permits the physician to visualize delivery of the composition to the vascular site via conventional techniques such as fluoroscopy.[1-8] Additionally, the use of water insoluble contrast agents is beneficial during posttreatment procedures to visualize the embolized mass during, for example, surgery or to monitor the disease condition and/or for retreatment purposes. Visualization is particularly necessary when using catheter delivery techniques in order to ensure both that the composition is being delivered to the intended vascular site and that the requisite amount of composition is delivered. Preferably, the water insoluble contrast agent has an average particle size of about 10 μm or less.[15]

SUMMARY OF THE INVENTION

As noted above, this invention is directed to methods for gynecologic embolotherapy by endovascular embolization with a fluid embolic composition. The methods provide for delivery of a fluid composition to a uterine vascular site which, *in situ*, forms a coherent solid mass which embolizes the blood vessel.

In a preferred embodiment, the fluid embolizing composition comprises a biocompatible polymer, a biocompatible solvent and a contrast agent. In a further preferred embodiment, the contrast agent is a water insoluble contrast agent characterized by having an average particle size of about 10 μm or less.

In another preferred embodiment, the fluid embolizing composition comprises a biocompatible prepolymer and a contrast agent. In a further preferred embodiment, the contrast agent is a water insoluble contrast agent characterized by having an average particle size of about 10 μm or less.

Accordingly, in one aspect the invention provides a method for gynecological embolization comprising:

delivering a microcatheter to a uterine artery of a female patient; and

delivering a sufficient amount of a fluid embolic material through said microcatheter under conditions wherein the fluid embolic material forms a coherent mass *in situ* thereby embolizing the blood vessel.

The uterine artery is preferably an artery leading to a uterine fibroid. The fluid embolic material is preferably an embolic composition comprising a biocompatible solvent, a biocompatible polymer and a contrast agent.

Methods further comprising the step of delivering a detectable agent, such as a contrast agent, through the catheter after it has been inserted into the artery and detecting the agent to confirm that the catheter has the proper placement prior to delivery of embolic material to the vessel are also provided.

DETAILED DESCRIPTION OF THE INVENTION

This invention is directed to novel gynecological embolization methods which deliver endovascularly a fluid embolic composition. These methods employ fluid compositions characterized by particle sizes of no more than 100 μm (preferably less than 10 μm) which are suited for treating uterine fibroids. Specifically, the fluid compositions used herein provides the benefits heretofore acknowledged while simultaneously providing for a coherent mass *in situ* thereby overcoming complications heretofore associated with the use of small particles.

However, prior to discussing this invention in further detail, the following terms will first be defined:

The term "embolizing" refers to a process wherein a material is injected into a blood vessel which fills or plugs the blood vessel and/or encourages clot formation so that blood flow through the vessel ceases. Embolization of the blood vessel is, therefore, important in preventing/controlling bleeding due to lesions (e.g., organ bleeding, gastrointestinal bleeding, vascular bleeding as well as bleeding associated with an aneurysm). In addition, embolization can be used to ablate diseased tissue (e.g., tumors, etc.) by cutting off its blood supply. Embolization may also be used to prevent blood loss during or immediately following surgery. Embolization of tumors may be performed preoperatively to shrink tumor size and to aid in visualization of the tumor as well as to prevent blood loss related to surgical procedures. Gynecological embolization refers to embolization used to control acute and chronic genital bleeding in a wide variety of obstetric and gynecological disorders, including uterine fibroids.

The term "biocompatible polymer" refers to polymers which, in the amounts employed, are non-toxic, chemically inert, and substantially non-immunogenic when used internally in the patient and which are substantially insoluble in blood. Suitable biocompatible polymers include, by way of example, cellulose acetates[2,6-7] (including cellulose diacetate[5]), ethylene vinyl alcohol copolymers[4,8], hydrogels (e.g., acrylics), polyacrylonitrile, polyvinylacetate, cellulose acetate butyrate, nitrocellulose, copolymers of urethane/carbonate, copolymers of styrene/maleic acid, and mixtures thereof.[9] Preferably, the biocompatible polymer is also non-inflammatory when employed *in situ*.

The particular biocompatible polymer employed is not critical and is selected relative to the viscosity of the resulting polymer solution, the solubility of the biocompatible polymer in the biocompatible solvent, and the like. Such factors are well within the skill of the art.

Preferred biocompatible polymers include cellulose diacetate and ethylene vinyl alcohol copolymer. Cellulose diacetate polymers are either commercially available or can be prepared by art recognized procedures. In a preferred embodiment, the number average molecular weight, as determined by gel permeation chromatography, of the cellulose diacetate composition is from about 25,000 to about 100,000 more preferably from about 50,000 to about 75,000 and still more preferably from about 58,000 to 64,000. The weight average molecular weight of the cellulose diacetate composition, as determined by gel permeation chromatography, is preferably from about 50,000 to 200,000 and more preferably from about 100,000 to about 180,000. As is apparent to one skilled in the art, with all other factors being equal, cellulose diacetate polymers having a lower molecular weight will impart a lower viscosity to the composition as compared to higher molecular weight polymers. Accordingly, adjustment of the viscosity of the composition can be readily achieved by mere adjustment of the molecular weight of the polymer composition.

Ethylene vinyl alcohol copolymers comprise residues of both ethylene and vinyl alcohol monomers. Small amounts (e.g., less than 5 mole percent) of additional monomers can be included in the polymer structure or grafted thereon provided such additional monomers do not alter the embolizing properties of the composition. Such additional monomers include, by way of example only, maleic anhydride, styrene, propylene, acrylic acid, vinyl acetate and the like.

Ethylene vinyl alcohol copolymers are either commercially available or can be prepared by art recognized procedures. Preferably, the ethylene vinyl alcohol copolymer composition is selected such that a solution of 6 weight percent of the ethylene vinyl alcohol copolymer, 35 weight percent of a tantalum contrast agent in DMSO has a viscosity equal to or less than 60 centipoise at 20°C. As is apparent to one skilled in the art, with all

other factors being equal, copolymers having a lower molecular weight will impart a lower viscosity to the composition as compared to higher molecular weight copolymers. Accordingly, adjustment of the viscosity of the composition as necessary for catheter delivery can be readily achieved by mere adjustment of the molecular weight of the copolymer composition.

As is also apparent, the ratio of ethylene to vinyl alcohol in the copolymer affects the overall hydrophobicity/hydrophilicity of the composition which, in turn, affects the relative water solubility/insolubility of the composition as well as the rate of precipitation of the copolymer in an aqueous solution (e.g., blood). In a particularly preferred embodiment, the copolymers employed herein comprise a mole percent of ethylene of from about 25 to about 60 and a mole percent of vinyl alcohol of from about 40 to about 75. These compositions provide for requisite precipitation rates suitable for use in embolizing blood vessels in gynecological embolization procedures.

The term "contrast agent" refers to a biocompatible (non-toxic) radiopaque material capable of being monitored during injection into a mammalian subject by, for example, radiography or fluoroscopy. The contrast agent can be either water soluble or water insoluble. Examples of water soluble contrast agents include metrizamide, iopamidol, iothalamate sodium, iodomide sodium, and meglumine.

The term "water insoluble contrast agent" refers to a water insoluble (i.e., has a water solubility of less than 0.01 mg/ml at 20°C), radiopaque material capable of being monitored during injection into a mammalian subject by, for example, radiography. Examples of water insoluble contrast agents include tantalum, tantalum oxide and barium sulfate, which are commercially available in the proper form for *in vivo* use. Methods for preparing such water insoluble biocompatible contrast agents having an

average particle size of about 10 μm or less are described below. Other water insoluble contrast agents include gold, tungsten and platinum.

The term "biocompatible solvent" refers to an organic material liquid at least at body temperature of the mammal in which the biocompatible polymer is soluble and, in the amounts used, is substantially non-toxic. Suitable biocompatible solvents include, by way of example, dimethylsulfoxide, analogues/homologues of dimethylsulfoxide, ethanol, acetone, and the like. Aqueous mixtures with the biocompatible solvent can also be employed provided that the amount of water employed is sufficiently small that the dissolved polymer precipitates upon contact with the blood. Preferably, the biocompatible solvent is dimethylsulfoxide (DMSO).

The term "encapsulation" as used relative to the contrast agent being encapsulated in the polymer precipitate is not meant to infer any physical entrapment of the contrast agent within the precipitate much as a capsule encapsulates a medicament. Rather, this term is used to mean that an integral coherent precipitate forms which does not separate into individual components.

The term "biocompatible prepolymer" refers to materials which polymerize *in situ* to form a polymer and which, in the amounts employed, are non-toxic, chemically inert, and substantially non-immunogenic when used internally in the patient and which are substantially insoluble in blood. Suitable biocompatible prepolymers include, by way of example, cyanoacrylates[10,11,12], hydroxyethyl methacrylate, silicon prepolymers, and the like. The prepolymer can either be a monomer or a reactive oligomer[12]. Preferably, the biocompatible prepolymer is also non-inflammatory when employed *in situ*.

Compositions

Endovascular embolization of uterine arteries using embolic compositions comprising small particles, such as PVA particles of about 150-600 μm, has been disclosed to provide benefits in the endovascular embolization of uterine arteries. However, these compositions are also linked to greater pelvic pain and potentially lead to endometriosis in the treated patients.[17]

In contrast, the compositions of this invention are fluid compositions characterized by the fact that these compositions do not contain particles having an average particle size larger than 100 μm (preferably having an average particle size of no more than 20 μm and still more preferably no more than 10 μm) which compositions form a coherent mass *in vivo*. In some cases such as when the composition employs a water soluble contrast agent, the composition does not need to contain any particles.

The fluid compositions employed in the methods of this invention are polymer or prepolymer compositions prepared by conventional methods whereby each of the components is added and the resulting composition mixed together until the overall composition is substantially homogeneous.

Fluid polymer compositions preferably comprise a biocompatible polymer, a biocompatible solvent and a contrast agent. Such compositions can be prepared by adding sufficient amounts of the biocompatible polymer to the biocompatible solvent to achieve the effective concentration for the polymer composition. Preferably, the polymer composition will comprise from about 2.5 to about 8.0 weight percent of the biocompatible polymer composition based on the total weight of the polymer composition and more preferably from about 4 to about 5.2 weight percent. If necessary, gentle heating and stirring can be used to effect dissolution of the biocompatible polymer into the biocompatible solvent, e.g., 12 hours at 50°C.

Sufficient amounts of the contrast agent are then added to the biocompatible solvent to achieve the effective concentration for the complete composition. Preferably, the composition will comprise from about 10 to about 40 weight percent of the contrast agent and more preferably from about 20 to about 40 weight percent and even more preferably about 30 weight percent. Insofar as the contrast agent may not be soluble in the biocompatible solvent (e.g., a water insoluble contrast agent), stirring is employed to effect homogeneity of the resulting suspension.

In order to enhance formation of the suspension, the particle size of the water insoluble contrast agent is preferably maintained at about 10 μm or less and more preferably at from about 1 to about 5 μm (e.g., an average size of about 2 μm). In one preferred embodiment, the appropriate particle size of the contrast agent is prepared, for example, by fractionation. In such an embodiment, a water insoluble contrast agent such as tantalum having an average particle size of less than about 20 microns is added to an organic liquid such as ethanol (absolute) preferably in a clean environment. Agitation of the resulting suspension followed by settling for approximately 40 seconds permits the larger particles to settle faster. Removal of the upper portion of the organic liquid followed by separation of the liquid from the particles results in a reduction of the particle size which is confirmed under an optical microscope. The process is optionally repeated until a desired average particle size is reached.

The particular order of addition of components to the biocompatible solvent is not critical and stirring of the resulting suspension is conducted as necessary to achieve homogeneity of the composition. Preferably, mixing/stirring of the composition is conducted under an anhydrous atmosphere at ambient pressure. The resulting composition is heat

sterilized and then stored preferably in sealed amber bottles or vials until needed.

Each of the polymers recited herein is commercially available but can also be prepared by methods well known in the art. For example, polymers are typically prepared by conventional techniques such as radical, thermal, UV, γ irradiation, or electron beam induced polymerization employing, as necessary, a polymerization catalyst or polymerization initiator to provide for the polymer composition. The specific manner of polymerization is not critical and the polymerization techniques employed do not form a part of this invention.

In order to maintain solubility in the biocompatible solvent, the polymers described herein are preferably not cross-linked.

Prepolymer compositions preferably comprise a biocompatible prepolymer and a contrast agent which can be prepared by adding sufficient amounts of the contrast agent to the solution (e.g., liquid prepolymer) to achieve the effective concentration for the complete composition. Preferably, the prepolymer composition will comprise from about 10 to about 40 weight percent of the contrast agent and more preferably from about 20 to about 40 weight percent and even more preferably about 30 weight percent. When the contrast agent is not soluble in the biocompatible prepolymer composition, stirring is employed to effect homogeneity of the resulting suspension. In order to enhance formation of the suspension, the particle size of the contrast agent is preferably maintained at about 10 μm or less and more preferably at from about 1 to about 5 μm (e.g., an average size of about 2 μm).

When the prepolymer is liquid, the use of a biocompatible solvent is not absolutely necessary but may be preferred to provide for an appropriate

viscosity, etc. in the embolic composition. Preferably, when employed, the biocompatible solvent will comprise from about 30 to about 90 weight percent of the biocompatible prepolymer composition based on the total weight of the prepolymer composition and more preferably from about 60 to about 80 weight percent. When a biocompatible solvent is employed, the prepolymeric composition typically comprises from about 10 to about 50 weight percent of the prepolymer based on the total weight of the composition.

In a particularly preferred embodiment, the prepolymer is a cyanoacrylate ester which is preferably employed in the absence of a biocompatible solvent. When so employed, the cyanoacrylate composition is selected to have a viscosity of from about 5 to about 20 centipoise at 20°C.

The particular order of addition of components is not critical and stirring of the resulting suspension is conducted as necessary to achieve homogeneity of the composition. Preferably, mixing/stirring of the composition is conducted under an anhydrous atmosphere at ambient pressure. The resulting composition is sterilized and then stored preferably in sealed amber bottles or vials until needed.

<u>Methods</u>

The compositions described above can then be employed in methods for the catheter assisted embolization of uterine arteries. In such methods, a sufficient amount of this composition is introduced into the selected artery via a catheter delivery means preferably under fluoroscopy so that upon precipitation of the polymer or polymerization of the prepolymer, the blood vessel is embolized. The particular amount of embolizing composition employed is dictated by the total volume of the vasculature to be embolized, the concentration of polymer/prepolymer in the composition,

the rate of precipitation (solids formation) of the polymer, etc. Such factors are well within the skill of the art.

One particularly preferred method for catheter delivering the embolizing compositions of this invention to the selected vascular site is via a small diameter medical catheter. The particular catheter employed is not critical provided that polymeric catheter components are compatible with the embolizing composition (i.e., the catheter components will not readily degrade in the embolizing composition). In this regard, it is preferred to use polyethylene in the catheter components because of its inertness in the presence of the embolizing composition described herein. Other materials compatible with the embolizing compositions can be readily determined by the skilled artisan and include, for example, other polyolefins, fluoropolymers (e.g., Teflon™), silicone, etc.

One particularly preferred method for the catheter injection of the polymer composition of this invention is described by Greff, et al., U.S. Patent Application Serial No. 08/730,701, filed October 11, 1996 which application is incorporated herein by reference in its entirety.

When introduced into the vascular site, the biocompatible solvent diffuses rapidly into the blood and a solid coherent mass (precipitate) forms *in situ* which precipitate is the water insoluble polymer with the contrast agent encapsulated therein. Without being limited to any theory, it is believed that initially, a soft gel to spongy solid precipitate forms upon contact with the blood. This precipitate then restricts blood flow, entrapping red cells thereby causing clot embolization of the blood vessel.

Utility

The methods described herein are useful in gynecological uterine artery embolization to prevent/control bleeding related to gynecological

and/or obstetrical conditions. Accordingly, these compositions find use in human female and other mammalian female subjects requiring such embolization of blood vessels. Additionally, the methods can be used in the reversible sterilization of mammalian female patients as described in concurrently filed applications by Evans, et al. [3,14].

The following examples are set forth to illustrate the claimed invention and are not to be construed as a limitation thereof.

EXAMPLES

Unless otherwise stated, all temperatures are in degrees Celsius. Also, in these examples and elsewhere, the following abbreviations have the following meanings:

cc	=	cubic centimeter
cm	=	centimeter
DMSO	=	dimethylsulfoxide
EVOH	=	ethylene vinyl alcohol copolymer
g	=	gram
in.	=	inch
kg	=	kilogram
min.	=	minute
mL	=	milliliter
sec.	=	seconds
μm	=	micron

Example 1

The purpose of this example is to demonstrate the preparation of a fluid embolic polymer composition useful in the methods of this invention.

Specifically, an EVOH polymer composition was prepared as follows:

Composition

A) 8 gm EVOH;

B) 30 gm tantalum having an average particle size of about 3 μm (narrow size distribution); and

C) 100 mL DMSO.

Component A) was added to Component C) at 50°C and stirred for 2 hrs. on a hot plate under an argon blanket. To this resulting composition was added Component B and the resulting mixture was mixed until homogeneous.

In this composition, the average particle size of the contrast agent was prepared by fractionation wherein tantalum, having an average particle size of less than about 20 μm, was added to ethanol (absolute) in a clean environment. Agitation of the resulting suspension was followed by settling for approximately 40 sec. to permit the larger particles to settle faster. Removal of the upper portion of the ethanol followed by separation of the liquid from the particles results in a reduction of the particle size which is confirmed under a microscope (Nikon Alphaphot™). The process was repeated, as necessary, until an average 3 μm particle size was reached.

Example 2

The purpose of this example is to illustrate a specific protocol for embolizing a mammalian uterine artery via the methods of this invention. This example employed a 60 kg human female (age 45).

The patient is anesthetized. The embolic composition of Example 1 above is shaken for about 4 min. until the contrast agent was fully dispersed. A 150 cm 3-French polyethylene microcatheter is placed through a femoral artery and directed to a uterine artery leading to a

uterine fibroid tumor using a 0.014 in. guidewire while confirming microcatheter placement by injection of water soluble contrast agent (e.g., Omnipaque™ available from Nycomed, Princeton, New Jersey). After placement, a syringe containing saline is connected to the luer hub of the microcatheter and the water soluble contrast agent is flushed from the microcatheter hub and body with about 5 cc of saline over an approximately 1 min. period with gentle pulsing at 1 cc increments. Afterwards, the syringe is removed and a cap is secured on the microcatheter luer hub.

Sterile DMSO (0.8 cc) is aspirated into a 1 cc syringe. The cap is removed from the microcatheter hub and the syringe fitted thereto. About 0.30 cc of DMSO is injected into the catheter to remove the saline therefrom.

While the DMSO is being prepared and injected, the embolic composition is shaken for about 4 min. to fully disperse the water insoluble contrast agent. A 1 cc syringe is then filled with the embolic composition through a 21 gage needle. As soon as the DMSO is injected, the syringe is removed and the balance of the DMSO used for overfilling and washing the luer hub.

Afterwards, the syringe containing the embolic composition is immediately connected to the catheter hub, making sure that there is no air in the hub during the connection. With the composition syringe pointing up to create a sharp interfacial boundary between the DMSO and the embolic composition, the first 0.25 cc is injected over a 1 min. period to displace the DMSO in the microcatheter and dilute the DMSO in the blood. Under fluoroscopy, the embolic composition is visible in the distal portion of the microcatheter body. The syringe tip is lowered and the embolic composition then injected as the clinical situation requires. The volume of

the embolic composition is monitored to ensure that the amount of embolic composition injected corresponded to the volume of the vascular space being filled. Upon completion of the embolic composition injection, the embolic syringe is gently aspirated to separate the catheter tip from the embolic composition mass. After a few seconds, the syringe plunger is released and the microcatheter withdrawn.

The embolic composition, upon injection into the uterine artery, forms a coherent mass which embolizes the uterine artery.

From the foregoing description, various modifications and changes in the composition and method will occur to those skilled in the art. All such modifications coming within the scope of the appended claims are intended to be included therein.

WHAT IS CLAIMED IS:

1. A method for gynecological embolization comprising:

delivering a microcatheter to a uterine artery of a female patient; and

delivering a sufficient amount of a fluid embolic material through said microcatheter under conditions wherein the fluid embolic material forms a coherent mass *in situ* thereby embolizing the blood vessel.

2. The method of Claim 1 wherein the blood vessel is a blood vessel of a uterine fibroid.

3. The method of Claim 1 further comprising the steps of:

(a) delivering a detectable agent through the catheter after it has been inserted into the vessel; and

(b) detecting the agent to confirm that the catheter has the proper placement in the vessel prior to delivery of embolic material.

4. The method of Claim 1 wherein the fluid embolic composition comprises a biocompatible polymer, a biocompatible solvent and a contrast agent.

5. The method of Claim 4 wherein the fluid embolic composition comprising:

(a) from about 2.5 to about 8.0 weight percent of a biocompatible polymer;

(b) from about 10 to about 40 weight percent of a water insoluble, biocompatible contrast agent having an average particle size of about 10 μm or less; and

(c) from about 52 to about 87.5 weight percent of a biocompatible solvent

wherein the weight percent of the polymer, contrast agent and biocompatible solvent is based on the total weight of the complete composition.

6. The method according to Claim 5 wherein said biocompatible solvent is selected from the group consisting of dimethylsulfoxide, ethanol and acetone.

7. The method according to Claim 6 wherein said biocompatible solvent is dimethylsulfoxide.

8. The method according to Claim 7 wherein said contrast agent is a water insoluble contrast agent selected from the group consisting of tantalum, tantalum oxide, tungsten and barium sulfate.

9. The method according to Claim 8 wherein said contrast agent is tantalum.

10. The method according to Claim 5 wherein said biocompatible polymer is selected from the group consisting of cellulose acetates, ethylene vinyl alcohol copolymers, hydrogels, polyacrylonitrile, polyvinylacetate, cellulose acetate butyrate, nitrocellulose, copolymers of urethane/carbonate, copolymers of styrene/maleic acid, and mixtures thereof.

11. The method according to Claim 10 wherein said biocompatible polymer is an ethylene and vinyl alcohol copolymer.

12. The method according to Claim 13 wherein said contrast agent has an average particle size of from 1 to 10 microns.

13. The method of Claim 1 wherein the fluid embolic composition comprises a biocompatible prepolymer and a contrast agent.

14. The method of Claim 13 wherein the fluid embolic composition further comprises a biocompatible solvent.

15. The method of Claim 13 wherein said contrast agent is a water insoluble contrast agent selected from the group consisting of tantalum, tantalum oxide, tungsten and barium sulfate.

16. The method according to Claim 15 wherein said contrast agent is tantalum.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/04398

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61M 31/00
US CL :604/508
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/898; 604/20, 49, 52, 53, 56, 508

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,667,767 A (GREFF et al) 16 September 1997, entire patent, especially claims 7-12.	1-11 --- 12-16
Y	CASTANEDA-ZUNIGA et al., Interventional Radiology, Volume 1, Third Edition, 1997, Vascular Embolotherapy, pages 29-103.	1-11 --- 12-16
A	VEDANTHAM, MD, et al., Uterine artery embolization: An underused method of controlling pelvic hemorrhage, American Journal Obstetrical Gynecology, 1997, Volume 176, Number 4, pages 938-948, see page 945.	1-16
A, P	US 5,851,508 A (GREFF et al) 22 December 1998, entire patent.	1-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 APRIL 1999	14 MAY 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JEREMY THISSELL Telephone No. (703) 305-5261

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/04398

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

STIC LIBRARY OFFICIAL SEARCH: MEDLINE, EMBASE, WPIDS, HCAPLUS, BIOSIS
Search Terms: embolization, therapeutic, leiomyoma, polymers, uterine diseases, vedantham, uterine artery, artificial embolism, embolize, embolotherapy, fibroid, uterus, uterine, hypertrophy, composition, tumour, contrast, vessel, vascular;